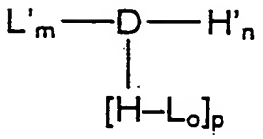
THE CLAIMS

We claim:

1. A drug-oligomer conjugate having the following general formula:



(Formula 1)

wherein

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids; and

m+n+p together have a value of at least one and not exceeding the total number of covalent bonding sites on D for the –H', –L and –H–L substituents;

the H–L bond(s) are hydrolyzable and the D–L' bond(s), when present, are hydrolyzable.

2. The drug-oligomer conjugate of claim 1 wherein m is 0 and p is at least 1.

3. The drug-oligomer conjugate of claim 1 wherein n is 0 and p is at least 1.

4. The drug-oligomer conjugate of claim 1 wherein m and n are each 0 and p is at least 1.

5. The drug-oligomer conjugate of claim 1 wherein p is 0 and m and n are each at least 1.

6. The drug-oligomer conjugate of claim 1 wherein the D–H and D–H' bonds, when present, are non-hydrolyzable.

7. The drug-oligomer conjugate of claim 1 wherein the D–L' bond, when present, is non-hydrolyzable.

8. The drug-oligomer conjugate of claim 1 wherein the D–H and D–H' bonds, when present, are independently selected from the group consisting of carbamate, amide and secondary amine.

9. The drug-oligomer conjugate of claim 1 wherein the H–L bond is selected from the group consisting of ester and carbonate.

10. The drug-oligomer conjugate of claim 1 wherein the D–L' bond is present and is selected from the group consisting of ester and carbonate.

11. The drug-oligomer conjugate of claim 1 wherein D is a biologically active polypeptide.

12. The drug-oligomer conjugate of claim 11 wherein the biologically active polypeptide has at least one available moiety for conjugation selected from the group consisting of XNH_2; –OH and XSH; and wherein at least one of the available moieties is conjugated to the H–L moiety.

13. The drug-oligomer conjugate of claim 11 wherein the biologically active polypeptide is selected from the group consisting of: adrenocorticotropic hormone; adrenocorticotropic hormone derivatives; ebiratide; angiotensin; angiotensin II; asparaginase; atrial natriuretic peptides; atrial sodium diuretic peptides; bacitracin; beta-endorphins; blood coagulation factors VII, VIII and IX; blood thymic factor; blood thymic factor derivatives; bone morphogenic factor; bone morphogenic protein; bradykinin; caerulein; calcitonin gene related polypeptide; calcitonins; CCK-8; cell growth factors; EGF; TGF-alpha; TGF-beta; PDGF; acidic FGF; basic FGF; cerulein; chemokines; cholecystokinin; cholecystokinin-8; cholecystokinin-pancreozymin; colistin; colony-stimulating factors; CSF; GCSF; GMCSF; MCSF; corticotropin-releasing factor; cytokines; desmopressin; dinorphin; dipeptide; dismutase; dynorphin; eledoisin; endorphins; endothelin; endothelin-antagonistic peptides; endotherins; enkephalin derivatives; enkephalins; epidermal growth factor; erythropoietin; follicle-stimulating hormone; gallanin; gastric inhibitory polypeptide; gastrin-releasing

polypeptide; gastrins; G-CSF; glucagon; glutathione peroxidase; glutathio-peroxidase; gonadotropin; gramicidin; gramicidines; growth factor; growth hormone-releasing factor; growth hormones; growth hormones; h-ANP; hormone releasing hormone; human chorionic gonadotrophin; human chorionic gonadotrophin β-chain; human placental lactogen; inhibitor; insulin; insulin-like growth factors; IGF-I; IGF-II; interferons; interleukins; intestinal polypeptide; kallikrein; kyotorphin; luliberin ; luteinizing hormone; luteinizing hormone-releasing hormone; lysozyme chloride; melanocyte stimulating hormone; melanocyte-stimulating hormone; melanophore stimulating hormone; mellitin; motilin; melanocyte stimulating hormone; muramyl; muramyldipeptide; nerve growth factor; nerve nutrition factors; NT-3; NT-4; CNTF; GDNF; BDNF; neuropeptide Y; neurotensin; oxytocin; pancreastatin; pancreatic polypeptide; pancreozymin; parathyroid hormone; pentagastrin; polypeptide YY; pituitary adenyl cyclase-activating polypeptides; platelet derived growth factor; polymixin B; prolactin; protein synthesis stimulating polypeptide; PTH-related protein; relaxin; renin; secretin; serum thymic factor; somatomedins; somatostatin derivatives; somatostatins; substance P; superoxide; superoxide dismutase; taftsin; tetragastrin; thrombopoietin; thymic humoral factor; thymopoietin; thymosin; thymostimulin; thyroid hormone releasing hormone; thyroid-stimulating hormone; thyrotropin releasing hormone TRH; trypsin ; tuftsin; tumor growth factor; tumor necrosis factor; tumour necrosis factor; tyrocidin; urogastrone; urokinase; vasactive intestinal polypeptide; vasoactive intestinal polypeptide; vasopressins; and functional equivalents of such polypeptides.

14. The drug-oligomer conjugate of claim 1 wherein D is an antigen from an organism or associated with a diesease state, selected from the group consisting of adenoviruses; anthrax; Bordetella pertussus; Botulism; bovine rhinotracheitis; Branhamella catarrhalis; canine hepatitis; canine distemper; Chlamydiae; Cholera; coccidiomycosis; cowpox; cytomegalovirus; cytomegalovirus; Dengue fever; dengue toxoplasmosis; Diphtheria; encephalitis; Enterotoxigenic E. coli; Epstein Barr virus; equine encephalitis; equine infectious anemia; equine influenza; equine pneumonia; equine rhinovirus; Escherichia coli; feline leukemia; flavivirus; Globulin; haemophilus influenza type b; Haemophilus influenzae; Haemophilus pertussis; Helicobacter pylori; Hemophilus; hepatitis; hepatitis A; hepatitis B; Hepatitis C; herpes viruses; HIV; HIV-1 viruses; HIV-2 viruses; HTLV; Influenza; Japanese encephalitis; Klebsiellae species; Legionella pneumophila; leishmania; leprosy; lyme disease; malaria immunogen; measles; meningitis; meningococcal; Meningococcal Polysaccharide Group A; Meningococcal Polysaccharide Group C; mumps; Mumps Virus; mycobacteria and; Mycobacterium tuberculosis; Neisseria; Neisseria gonorrhoeae; Neisseria

meningitidis; NonA NonB; ovine blue tongue; ovine encephalitis; papilloma; parainfluenza; paramyxovirus; paramyxoviruses; Pertussis; Plague; Pneumococcus; Pneumocystis carinii; Pneumonia; Poliovirus; Proteus species; Pseudomonas aeruginosa; rabies; respiratory syncytial virus; rotavirus; Rubella; Salmonellae; schistosomiasis; Shigellae; simian immunodeficiency virus; Smallpox; Staphylococcus aureus; Staphylococcus species; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus species; swine influenza; tetanus; Treponema pallidum; Typhoid; Vaccinia; varicella-zoster virus; and Vibrio cholerae.

15. The drug-oligomer conjugate of claim 1 wherein D is insulin or a functional equivalent thereof.

16. The drug-oligomer conjugate of claim 1 wherein H and H' are independently selected from the group consisting of straight or branched PEG_{1-130} and sugars.

17. The drug-oligomer conjugate of claim 1 wherein H and/or H' is a sugar, independently selected from the group consisting of amino sugars, glycerol and natural monosaccharides.

18. The drug-oligomer conjugate of claim 1 wherein L is selected from the group consisting of: alkyl groups having 2 to 24 carbons; fatty acids having 4 to 26 carbons; cholesterol and adamante.

19. The drug-oligomer conjugate of claim 1 wherein H-L comprises a subunit selected from the group consisting of:

$CH_3(CH_2)_n(OC_2H_4)_mOH$ (Formula 3);

wherein n=3 to 25 and m=1 to 7;

$CH_3(CH_2)_n(OC_2H_4)_mOCH_2CO_2H$ (Formula 4);

wherein n=3 to 25 and m=1 to 6;

$CH_3(CH_2)_nCX(OC_2H_4)_mOH$ (Formula 5);

wherein n=3 to 25 , m=1 to 7 and X=O;

$R\text{-}(OC_2H_4)_mCH_2CO_2H$ (Formula 6)

wherein m=0 to 5 and R=cholesterol or adamantane; or

$R\text{-}OCO(C_2H_4O)_mCH_2CO_2H$ (Formula 7);

wherein m=0 to 14;

$CH_3(CH_2—CH=CH)_6(CH_2)_2CH_2(OC_2H_4)_mOH$ (Formula 8);

wherein m=0 to 7;

$CH_3(CH_2—CH=CH)_6(CH_2)_2CX(OC_2H_4)_mOH$ (Formula 9);

wherein m=1 to 7 and X=N or O.

20. A pharmaceutical composition comprising the drug-oligomer conjugate of claim 1 in association with a pharmaceutical carrier.

21. A pharmaceutical composition comprising the drug-oligomer conjugate of claim 1 in association with an emulsion.

22. A pharmaceutical composition comprising the drug-oligomer conjugate of claim 1 in association with a microemulsion.

23. A drug-oligomer conjugate having the following general formula:

$$D\text{–}[(H\text{–}S_n)\text{–}L_o]_p \qquad \text{(Formula 11)}$$

wherein

D is a therapeutic drug moiety;

H is a hydrophilic moiety selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids; and

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can be attached to H';

o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to S;

p is a number from 1 to the maximum number of covalent bonding sites at which $-[(H-S_n)-L_o]_p$ can be attached to D; and

the S–L and/or S–H bond is hydrolyzable.

24. The drug-oligomer conjugate of claim 23 wherein D is insulin or a functional equivalent thereof.

25. A drug-oligomer conjugate having the following general formula:

$$D-[(H-S_n-H'_q)-L_o]_p \qquad \text{(Formula 12); and}$$

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids; and

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

n is a number from 1 to the maximum number of covalent bonding sites at which S can be attached to H;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can be attached to S;

o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to S;

p is a number from 1 to the maximum number of covalent bonding sites at which $-[(H-S_n-H'_q)-L_o]_p$ can be attached to D; and

the S–H and/or S–H' bond(s) are hydrolyzable.

26. The drug-oligomer conjugate of claim 25 wherein D is insulin or a functional equivalent thereof.

27. A drug-oligomer conjugate having the following general formula:

$$D-[(H-H'_q-S_n)-L_o]_p \qquad \text{(Formula 13)}$$

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids; and

S is a spacer group selected from the group consisting of sugars, carbohydrates and glycerol;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can be attached to H;

n is a number from 1 to the maximum number of covalent bonding sites at which S can be attached to H';

o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to S; and

the H–H' bond is hydrolyzable.

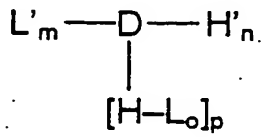
28. The drug-oligomer conjugate of claim 27 wherein D is insulin or a functional equivalent thereof.

29. The drug-oligomer conjugate of claim 27 wherein D is insulin or a functional equivalent thereof and H is PEG_{2-7}.

30. The drug-oligomer conjugate of claim 27 wherein D is insulin or a functional equivalent thereof and H is PEG_3.

31. A method for solubilizing a drug in a microemulsion comprising:

a) providing a drug-oligomer conjugate having a formula:



(Formula 1)

where

D is a therapeutic drug moiety;

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

m+n+p are at least one and do not exceed the number of covalent bonding sites for such substituents;

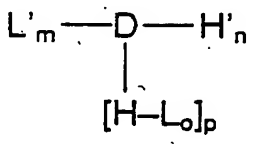
o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to H;

the H–L bond and the D–H bond, when present, are hydrolyzable:

b) bringing the drug-oligomer conjugate of a) into association with a microemulsion.

32. The drug-oligomer conjugate of claim 32 wherein D is insulin or a functional equivalent thereof.

33. A method for providing an active drug-hydrophile conjugate to a situs of a subject, the method comprising administering to the subject an inactive drug-oligomer conjugate having a formula:



(Formula 1)

wherein

H and H' are each a hydrophilic moiety, independently selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L and L' are each a lipophilic moiety, independently selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

m+n+p are at least one and do not exceed the number of covalent bonding sites for such substituents;

o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to H;

the H–L bond and the D–H bond, when present, are hydrolyzable in the subject to provide the active drug-amphiphile conjugate.

34. The method of claim 33 wherein D is insulin or a functional equivalent thereof.

35. The method of claim 33 wherein H is a straight or branched PEG polymer having from 2 to 7 PEG subunits.

36. The method of claim 33 wherein H is a straight or branched PEG polymer having from 3 to 6 PEG subunits.

37. The method of claim 34 wherein H is a straight or branched PEG polymer having from 2 to 7 PEG subunits.

38. The method of claim 34 wherein H is a straight or branched PEG polymer having from 3 to 6 PEG subunits.

39. A method for providing an active drug–PEG conjugate to a situs of a subject, wherein the drug component of the drug–PEG conjugate is selected from the group consisting of insulin and functional equivalents of insulin, and wherein the drug-PEG conjugate has enhanced activity in comparison with a corresponding unconjugated insulin molecule, the method comprising administering to the subject an inactive drug–PEG–lipophile conjugate having a formula:

$$D–[(H–H'_q)–L_o]_p \quad \text{(Formula 10)}$$

wherein

D is a therapeutic moiety;

H is a straight or branched PEG polymer having from 2 to 7 PEG subunits;

H' is a straight or branched PEG polymer having from 0 to 130 PEG subunits;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids;

q is a number from 1 to the maximum number of covalent bonding sites at which H' can be attached to H;

o is a number from 1 to the maximum number of covalent bonding sites at which L can be attached to H';

p is a number which is at least 1 and does not exceed the number of covalent bonding sites at which $[(H–H'_q)–L_o]$ can be attached to D;

the H–H' bond and/or the H–L bond are hydrolyzed in the subject to provide the active drug-amphiphile conjugate.

40. The method of claim 39 wherein H is a straight or branched PEG polymer having from 2, 3, 4, 5, or 6 PEG subunits.

41. The method of claim 39 wherein the drug- PEG_{2-10}-lipophile is administered in association with a pharmaceutically acceptable carrier as a pharmaceutical composition.

42. The method of claim 39 wherein the drug- PEG_{2-10}-lipophile is administered in association with an emulsion as a pharmaceutical composition.

43. The method of claim 39 wherein the drug- PEG_{2-10}-lipophile is administered in association with a microemulsion as a pharmaceutical composition.

44. A drug-oligomer conjugate having the following general formula:

$$D–[(H–H'_q)–L_o]_p \quad \text{(Formula 10)}$$

wherein:

D is a therapeutic drug moiety;

H and H' are hydrophilic moieties, individually selected from the group consisting of straight or branched PEG polymers having from 2 to 130 PEG subunits, and sugars;

L is a lipophilic moiety selected from the group consisting of alkyl groups having 2-24 carbon atoms, cholesterol, and fatty acids; and

the H–H' bond is hydrolyzable and the H'–L bond is not hydrolyzable;

q is a number from 1 to the maximum number of covalent bonding sites on H at which an H' can be attached to H;

o is a number from 1 to the maximum number of covalent bonding sites at which an L substituent can be attached to H'; and

p is a number from 1 to the maximum number of covalent bonding positions at which $–[(H–H'_q)–L_o]_p$ can be attached to D.

45. The drug-oligomer conjugate of claim 44, wherein D, H, H', and L are selected and arranged such that the drug-oligomer conjugate is amphiphilic.

46. The drug-oligomer conjugate of claim 44, wherein D is insulin or a functional equivalent thereof and H is PEG_{2-7}.

47. The drug-oligomer conjugate of claim 44, wherein D is insulin or a functional equivalent thereof and H is PEG_3.

48. The drug-oligomer conjugate of claim 45, wherein D is insulin or a functional equivalent thereof and H is PEG_{2-7}.

49. The drug-oligomer conjugate of claim 45 wherein D is insulin or a functional equivalent thereof and H is PEG_3.